cytokine, cytokine agonist, cytokine antagonist, monoclonal antibody, antigen-binding antibody fragment, immunotoxin, immunosuppressant, ischemia-protective agent, adrenergic agent, boron compound, anticonvulsant, anti-trauma agent or diagnostic agent.

Claim 320. (new) A pharmaceutical composition comprising a combination of YC-1 formulated together in a pharmaceutically acceptable solution together with a medicant for delivery by intravascular infusion or injection, wherein the medicant is a DNA expression vector, viral vector, protein, oligonucleotide or nucleotide analog.

REMARKS

The Examiner has entered the request for continued examination (RCE) filed on January 1, 2004. The Examiner objects however to the claims presented in the RCE as independent and distinct from the invention originally claimed and examined. The Examiner notes that the RCE claims (now pending after entry) are drawn to a method of delivering a medicant to an abnormal brain region or a malignant tumor in a mammalian subject by administering a direct agonist of an ATP-sensitive potassium channel to increase the permeability to the medicant of the region, a pharmaceutical composition and a kit comprising a direct agonist of an ATP-sensitive potassium channel. In contrast, the Examiner notes that the originally elected and examined claims are drawn to a method of delivering a medicant to an abnormal brain region or malignant tumor in a mammalian subject by administering an in vivo activator of a calcium-activated potassium channel to the mammal, wherein the activator is an activator of soluble guanylyl cyclase, and as well as a pharmaceutical composition and a kit comprising the activator of soluble guanylyl cyclase.

In response to the Examiner's objection, the Applicants desire to amend the pending claims. The amended claims are directed to a method of delivering a medicant to an abnormal brain region or malignant tumor in a mammalian subject by administering a direct agonist of calcium-activated potassium channel to increase the permeability to the medicant of the region, a pharmaceutical composition and a kit comprising a direct agonist of a calcium-activated potassium channels. Thus, the amended claims and the claims as previously examined are both directed to calcium-activated potassium channels. Applicants reserve the right to pursue the

subject matter of the previously pending claims (i.e., direct agonists of ATP-sensitive potassium channels) in a continuation application. Applicants have further amended the claims to (i) to divide the subject matter of prior dependent claims covering a number of medicants, disease states and other subject matter into separate claims; and (ii) to correct certain obvious typographical and spelling errors.

The Examiners attention is directed to the fact that the amended claims are distinct from the previously examined claims because the amended claims are drawn to direct agonists of calcium-activated potassium channels. In contrast, the previously examined claims are directed to in vivo activators of calcium-activated potassium channels, wherein such activators are activators of soluble guanylyl cyclase. Both direct agonists and activators of soluble guanylyl cyclase cause calcium-activated potassium channels to open, producing an increase in permeability. However, direct agonists produce this result directly (i.e., by binding to the calcium-activated potassium channel and thereby causing it to open), while activators of soluble guanylyl cyclase produce this result indirectly (i.e., by initiating a signaling cascade that ultimately results in the opening of the calcium-activated potassium channel).

Before entry of the amendments contained herein, Claims 1-3, 12, 13, 18-24, 48, 57-60, 65-71, 135-137, 151-153 and 190-286 are pending in the application. After entry of the amendment, Claims 1-3, 12-13, 18-24, 48, 57-60, 65-71, 135-137, 151-153, 195-234, 240-272, 278-284 and 287-320 are pending. Claims 4-11, 14-17, 25-47, 49-56, 61-64, 72-134, 138-150, 154-194, 235-239, 273-277 and 285-286 have been cancelled.

Claims 1-3, 12-13, 18-24, 195-234, and 287-292 are directed to a method of delivering a medicant to an abnormal brain region in a mammalian subject comprising administering to a mammalian subject having an abnormal brain region a direct agonist of a calcium-activated potassium channel to increase the permeability to the medicant of the region. Claims 287-288 are newly presented, and drawn to particular direct agonists of calcium-activated potassium channels (i.e., NS1619 and EBIO). Support for these claims can be found in the specification, for example on pages 13-14. Claims 289-292 are also newly presented, and directed to particular medicants, including DNA expression vectors, viral vectors, oligonucleotides and nucleotide analogs. Support for these claims can be found in the specification, for example on page 21.

Claims 48, 57-60, 65-71, 240-272, 293-298 are directed to a method of delivering a medicant to a malignant tumor involving administering a direct agonist of a calcium-activated

potassium channel and a medicant. Claims 293-294, drawn to particular direct agonists (i.e., NS1619 and EBIO), are newly presented and supported as described above. Newly presented Claims 295-298 are directed to particular medicants, including DNA expression vectors, viral vectors, oligonucleotides and nucleotide analogs, and are supported as described above.

Claims 135-137, 151-152, 278-282, 299-300 are directed to a pharmaceutical composition including a combination of a direct agonist of a calcium-activated potassium channel agonist and a medicant selected from the group consisting of therapeutic cytotoxic agents and anticancer chemotherapeutic agents. Newly presented Claims 299-300 are drawn to particular direct agonists (i.e., NS1619 and EBIO) which are supported as described above.

Claims 153, 301-302 are directed to a kit for delivering a medicant to an abnormal brain region including a direct agonist of a calcium-activated potassium channel. Newly presented Claims 301-302 are drawn to particular direct agonists (i.e., NS1619 and EBIO) which are supported as described above.

Claims 283 and 284 are directed to a pharmaceutical composition including a combination of a direct agonist of a calcium-activated potassium channel and a medicant.

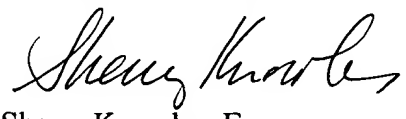
New independent Claim 303 and dependent claims related thereto (i.e., Claims 304-313) cover a method of delivering a medicant to an abnormal brain region or malignant tumor in a mammalian subject by administering YC-1 (an activator of soluble guanylyl cyclase) to increase the permeability to the medicant of the region. Support for these claims can be found in the specification, for example on page 14. Claim 303 is limited over a Claim 162, previously examined but cancelled in the RCE, directed to a method of delivering a medicant to an abnormal brain region or malignant tumor in a mammalian subject by administering an activator of soluble guanylyl cyclase selected from the group consisting of YC-1 and NONOate to increase the permeability of the medicant to the region.

New independent Claim 314 and dependent claims related thereto (i.e., Claims 315-318) are directed to a pharmaceutical composition including a combination of YC-1 and a therapeutic cytotoxic agent or anticancer chemotherapeutic drug. Support for this claim can be found in the specification, for example on page 14.

New independent Claims 319-320 are directed to pharmaceutical compositions including a combination of YC-1 and a medicant. Support for this claim can be found in the specification, for example on page 14.

Applicants believe that the amended claims presented herein, together with the Declaration of Dr. Nagendra S. Ningaraj submitted with the RCE, are fully responsive to the Final Office Action mailed January 15, 2003. If there are any issues that can be resolved with an Examiner's Amendment or a telephone conference, please contact the undersigned attorney at 404.572.3541.

Respectfully submitted,



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